Biological Research Evolves at Livermore

"We count it as a privilege to do everything we can to assist our medical colleagues in the application of these new tools to the problems of human suffering."

—Ernest O. Lawrence, in his acceptance speech for the 1939 Nobel Prize for Physics, speaking of practical applications for his cyclotron.

As the Laboratory celebrates its 50th anniversary, its biological research program begins its 40th year. Established in May 1963 by the Atomic Energy Commission, the program's original mission was to investigate the effects of ionizing radiation on humans.

Today, Livermore's biological research extends far beyond studying the effects of radiation. A primary emphasis is countering the terrorist threat that grips our nation. The anthrax scares in the fall of 2001 alerted us to the danger of bioterrorism and heightened the need for fast, accurate, inexpensive methods to detect biological warfare agents. Fortunately, long before last fall, Livermore was a leader in developing innovative methods and technologies for early detection of bioterrorism threats. Since the attack, the Laboratory has intensified its efforts in this area so vital to national security.

Radiation effects and bioterrorism response have more in common than might at first be apparent. The link is DNA, the genetic code of all living things. Technologies developed during Livermore's studies of how radiation affects DNA contributed to the founding of the Human Genome Project, the largest biological research project ever undertaken. Since the working draft of the human genome was completed in 2000, the genomes of many other animals and microbes have been sequenced. Sequencing the DNA of bioagent microbes supplies the basis for DNA signatures that are being put to work in new detectors.

Livermore's early analysis of DNA damage has evolved into long-term research in several areas important to human health. Research on radiation exposure resulted in new assays that were first used to evaluate genetic changes in atom bomb survivors in Japan and later applied to understanding the exposures incurred by workers who cleaned up the Chernobyl nuclear power plant after the 1986 accident. Several of these tools have broad application in bioscience. Another research area focuses on how DNA repairs itself. One project analyzes the ways that damaged DNA affects sperm during critical stages of reproduction. Another examines how cooking certain foods produces chemicals that damage DNA. Along the way,

Livermore bioresearchers have pioneered many new tools and methods for bioscience research, often collaborating with physicists, chemists, engineers, and computer scientists.

In 1972, Roger Batzel, then Laboratory director, said, "I personally view Bio-Med as an area which could well grow. It's been a relatively small program, but I think it could develop into one of the strengths of the Laboratory."

Batzel could hardly imagine how dramatically Livermore's nascent biomedical program would grow and change. The recent proposal to establish a homeland security center of excellence at Livermore owes much to the distinguished efforts over the years of many Livermore biological research scientists.

During the 1983 celebration of the 20th anniversary of biomedical research at Livermore, then Laboratory Director Roger Batzel, Associate Director Mort Mendelsohn, and former Program Director John Gofman viewed the work of bioscientist Laurie Gordon.

Of Chromosomes and DNA

Biological studies at Livermore have two major origins. One was the advent of thermonuclear testing in the Pacific Ocean during the mid-1950s. The other was Project Plowshare, which was devoted to the peaceful uses of nuclear weapons for stimulating underground natural gas production, mining, blasting out harbors, and perhaps even creating a new Panama Canal. Testing in the Pacific and in the Soviet Union had made radioactive fallout a major public issue. With Plowshare's vision of nuclear explosions near populated areas for routine engineering tasks, nuclear contamination became a more direct concern.

John Gofman, a professor of medical physics at the Donner Laboratory of the University of California at Berkeley, was recruited to set up the new program. As it happened, Project Plowshare was largely shelved by the time Gofman started working. "But he studied the dose to humans anyway, with an emphasis on radiation safety," says Mort Mendelsohn, who followed Gofman as leader of the biomedical research program.

By 1963, the scientific community suspected that DNA was the cellular part most sensitive to radiation damage. Gofman had already become involved in cytogenetics, the study of chromosomes, a field that was making major advances at the time. According to Mendelsohn, "Gofman wanted to measure chromosomes for a reason that was way ahead of its time." Many researchers were growing cancer cells in culture, and Gofman suggested examining the chromosomes in these cells to see what changes they had in common. He developed a method of analyzing chromosomes by measuring their length. It proved to lack adequate sensitivity, but his work set the stage for future cytogenetics progress at Livermore.

In 1974, two years after Mendelsohn's arrival, Livermore scientists made history when they successfully measured and sorted hamster chromosomes using flow cytometry. In humans and other complex organisms, DNA is packaged into chromosomes. Humans have 23 pairs, or 46 total. With flow cytometry, researchers could for the first time automatically

identify and sort individual chromosomes or whole cells for subsequent assessment.

During the 1970s and 1980s, the Laboratory made rapid advances in flow cytometry and was for many years a premier institution for cytometric research. In fact, Mendelsohn and other Livermore scientists founded the Society for Analytic Cytology, now the International Society for Analytic Cytology. The journal *Cytometry*, first issued in 1980, was published from Livermore for many years. More recently, Livermore engineers miniaturized flow cytometry in microfluidic systems that support medical devices and detectors for biological and chemical agents. (See *S&TR*, November 1999, pp. 10–16.)

By 1979, scientists had learned how to sort human chromosomes, which are much smaller and more varied than the hamster's. By 1984, says Mendelsohn, "We had increased our proficiency and confidence in flow cytometry such that we could separately identify and study each of the human chromosomes." This ability, combined with worldwide developments in recombinant DNA technology, led to the Livermore–Los Alamos project to build human chromosome-specific DNA libraries.

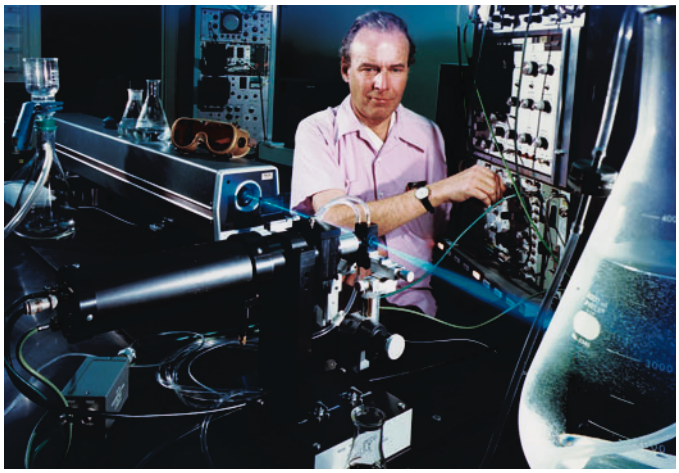
"The development of chromosome-specific libraries was important," continues Mendelsohn. "At that time, sequencing technology was slow and primitive. The thought of sequencing the entire human DNA was overwhelming. But when the sequencing process could be broken down into smaller pieces—chromosomes—it became a possibility."

At a 1984 meeting, molecular geneticists from around the world brainstormed the potential for DNA-oriented methods to detect heritable mutations in the children of people who survived the atom bombs in Japan. Many of the questions were so challenging that large-scale, detailed genomic sequence analysis would be needed to even attempt to answer them. (To this day, the basic question of how often heritable mutations occur remains unanswered.) Recognizing the classes of problems that require large-scale, detailed sequence data helped inspire the idea of sequencing the entire human genome.

In 1986, the Department of Energy launched a major initiative to completely decipher the human genetic code. A year later, Livermore researchers began to study chromosome 19, which they had earlier learned was home to several genes important for DNA repair. DOE joined forces with the National Institutes of Health in 1990 to kick off the Human Genome Project.

In 1992, Anthony Carrano became associate director of biomedical research. Carrano, who had been studying chromosomes and DNA since arriving at Livermore in 1973, was instrumental in building the Laboratory's human genome efforts, particularly sequencing. In 1996, he helped form the Joint Genome Institute (JGI). This collaboration of the Livermore, Berkeley, and Los Alamos national laboratories pooled resources to form a production facility to sequence human chromosomes 5, 16, and 19 for the international Human Genome Project.

During the 1990s, sequencing technologies matured, becoming ever more automated. Sequencing speed increased rapidly. A working draft of the three chromosomes was completed in April 2000, a year ahead of a greatly accelerated



Marv Van Dilla, an expert in flow cytometry, came to Livermore from Los Alamos in 1972. Shown here in 1973, Van Dilla was instrumental in establishing the Laboratory's preeminence in cytometric research. Livermore was the first to use flow cytometry to sort chromosomes.

Bioscientists Anthony Carrano, who later became associate director, and Larry Thompson in 1978. They had just developed a quick and efficient test to detect damage to genes. The test was based on a finding by Livermore scientists that there is a direct relationship between hard-to-spot gene mutations and an easily recognized process that occurs during cell division. Today, Thompson performs research on DNA repair processes.

schedule set just 18 months earlier. (See *S&TR*, April 2000, pp. 4–11.) This accomplishment was a major step toward understanding DNA and its functions and a significant contribution to the completion of draft sequences of the entire genome in June 2000.

Still Much to Learn

In the excitement over the completed sequence of the human genome, it is easy to forget that this step is just a prologue. The next step is to identify all of our genes and determine what they do and how they do it. Comparative genomics—in which the genomes of different species are compared—is helpful. Mouse DNA is useful because about 99 percent of a mouse's genes are similar to human genes. Comparing how these genes work in mice and how they are activated under different conditions tells us much about our own genes. A JGI team led by Livermore biologist Lisa Stubbs compared human chromosome 19 with similar sections of the mouse DNA to understand the functional significance of DNA sequences. (See *S&TR*, May 2001, pp. 12–20.) Stubbs notes, "Imagine taking human chromosomes, shattering them into pieces of varying lengths, and putting them back together in a different order. That's what mouse chromosomes look like." The Japanese pufferfish (fugu) has also been sequenced because its genome is a compact version of our own.

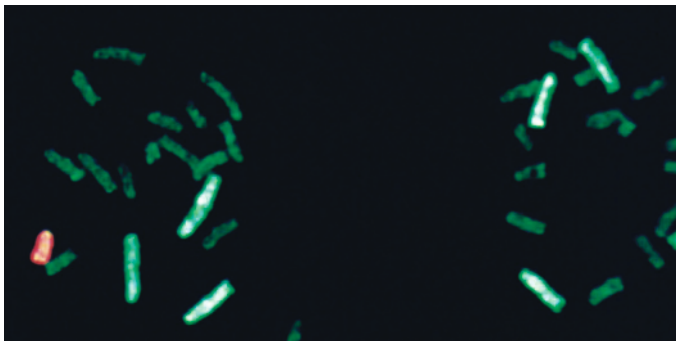
Another outgrowth of the Human Genome Project is proteomics, the study of the 100,000 or so proteins that are generated by our DNA. Proteins are the building blocks of our cells and of the molecular machinery that runs our tissues, organs, and bodies. Understanding how proteins operate is essential to understanding how biological systems work.

X-ray crystallography and nuclear magnetic resonance spectroscopy are two tools Livermore is using to determine the three-dimensional structure of proteins at the atomic level. From that structure, computational methods can attempt to model a protein's function. But determining the structure protein by protein would take years of research to complete. Instead, Livermore scientists are using the minimal data available in computational models to try to predict a protein's structure.

Measuring Radiation Effects

In the first 10 years of Livermore's biological research program, scientists searched for biological measurements that would indicate the radiological dose to which an individual had been exposed. Livermore developed several biological dosimeters to detect and measure changes in human cells,

Researcher Laura Chittenden is shown with a mouse. Mouse DNA, 99 percent of which is similar to human DNA, is being compared to human DNA to help uncover clues to gene regulation and control.



Chromosome painting is the process scientists use to fluorescently label small pieces of DNA from a chromosome-specific library. These chromosome-specific fluorescent probes bind to complementary sequences of the target chromosome and, when viewed under a microscope using fluorescent light, can reveal a targeted gene along a chromosome. This photo is of chromosomes from one-day-old mouse embryos. The bright green chromosomes are chromosomes 1, 2, 3, and X. The orange one is chromosome Y.

significantly advancing the study of human radiation biology and toxicology. The first was the glycophorin-A assay that detects residual mutations in human red blood cells from exposure to radiation decades earlier. Its first use was on atom bomb survivors in Japan.

Work on the glycophorin-A assay begat one of Livermore's first biotechnology projects. In the late 1970s, Laboratory biologists needed antibodies that recognize the subtle distinction between normal and mutant red blood cells. Researchers rolled up their sleeves and began to produce these and many other made-to-order monoclonal antibodies (antibodies derived from a single cell) with a range of potential uses—from detecting sickle cell anemia to evaluating how fast cancer cells are growing. Livermore is no longer in the production mode, but many of its monoclonal antibodies were commercially produced and used by others.

Another important technology developed at Livermore in the mid-1980s is chromosome painting. Scientist Dan Pinkel was instrumental in developing this technology, and the patent for this work has been one of the most lucrative in Livermore's patent portfolio for the past several years.

When first developed, chromosome painting was used to identify DNA damage in which the ends of two chromosomes break off and trade places with each other. These "reciprocal translocations" are one of the distinguishing effects of radiation damage to DNA. Using chromosome painting, scientists can see and count translocations between two differently painted chromosomes to determine a person's likely prior exposure to ionizing radiation. This method of identifying translocations is 10 to 100 times faster than it was before, with greatly increased reliability.

Biology Meets the Computer—The Early Days

Throughout its 50-year history, the Laboratory has pioneered the use of powerful computers to solve complex scientific problems. Challenges in biological research were no exception.

In the mid-1960s, new work on the dynamics of cell multiplication made use of computer codes first developed for Livermore's weapons program. Part of an effort to design an optimal radiation dosage program for cancer therapy, the study included an ingenious calculation system using computer codes to simulate cell activity.

A remarkable combination of an electron microscope and a computer in 1968 produced dramatic three-dimensional images of organelles, tiny working parts within the cell nucleus. Using essentially the same process the human brain uses to produce three-dimensional images from two flat pictures—one taken with each eye—the computer took 12 electron microscope shots, integrated the information, and created three-dimensional images of the organelles that were 50,000 times their real size. The feat had never before been accomplished.

By 1973, Livermore's cytophotometric data conversion system (CYDAC) was attracting interest when it showed that it could measure the DNA in individual chromosomes to great sensitivity. CYDAC studies showed unsuspected small differences in chromosomal DNA content among supposedly normal individuals.

In its first clinical application in 1974, CYDAC confirmed a suspected chromosome abnormality in a patient with chronic myelogenous leukemia (CML). In the early 1960s, scientists discovered that CML was invariably associated with a loss of genetic material from a portion of chromosome 22. This aberration was rarely found otherwise. About 10 years later, researchers at the University of Chicago found an excess of chromosomal matter on chromosome 9 in the same patients. They suspected that the lost material from chromosome 22 had been captured by chromosome 9. It took CYDAC's unprecedented precision to confirm that hypothesis and set cancer researchers on the track of other DNA translocations.

Bioengineers at Livermore combined mechanical skills with an understanding of biology to design the cytophotometric data converter (CYDAC), a highly sensitive diagnostic instrument that measures the amount of DNA in chromosomes. In this 1976 photograph, bioresearcher Linda Ashworth uses CYDAC to scan chromosomes from a mammalian cell.

A third dosimetry method measures the frequency of mutations in the hypoxanthine phosphoribosylantransferase (HPRT) gene in lymphocytes. This assay was developed elsewhere, but since the 1980s, researchers led by biological scientist Irene Jones have greatly expanded understanding of the assay's ability to detect DNA damage from ionizing radiation.

Immediately after the 1986 Chernobyl nuclear accident, the glycophorin-A assay was put to work to screen cleanup workers for their exposures. Years later, bioscientists used the HPRT assay and chromosome painting to measure mutations and alterations in lymphocytes to reconstruct the doses received. (See *S&TR*, September 1999, pp. 12–15.)

To Your Health

A natural extension of studying the effects of ionizing radiation on humans was to explore how radiation and chemicals interact with human genetic material to produce cancers, mutations, and other adverse effects.

In the face of damaging toxins, DNA is able to repair itself—up to a point. How DNA repairs itself has been a focus of ongoing research under bioscientist Larry Thompson almost since the Laboratory began to study DNA damage. Livermore chose to sequence chromosome 19 as part of the Human Genome Project because its properties suggested that it was gene-rich, which proved to be an accurate prediction. Chromosome 19 has the highest gene density of any human chromosome. It was also an apt choice because Livermore researchers had earlier discovered that three genes on chromosome 19 are involved in the repair of DNA damaged by radiation or chemicals. In studies of the Chernobyl cleanup workers, a goal has been to understand why the same dose of radiation has different effects on the cells of individuals. Identifying the differences in DNA repair gene sequence and function for different individuals is key.

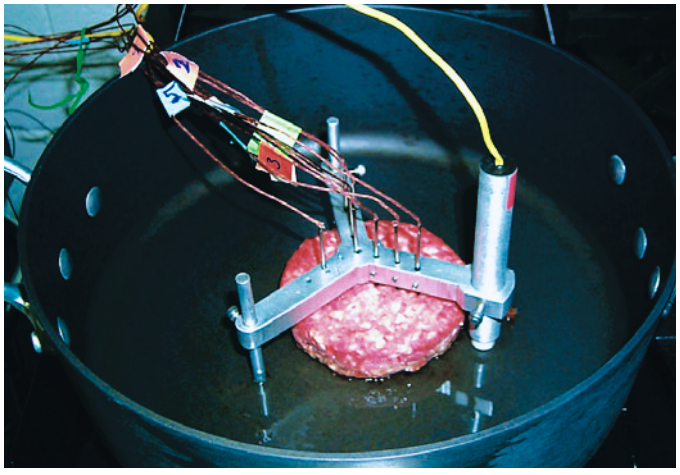
In the 1970s, Livermore's growing expertise in flow cytometry enabled researchers to analyze and sort sperm for the first time. Using this approach, scientists could begin to study the effects of pollutants on DNA during critical stages of sperm formation. Under the leadership of biophysicist Andrew Wyrobek, Livermore has developed several powerful molecular methods to visualize individual chromosomes in sperm and to detect genetic defects in embryos. (See *S&TR*, November/December 1995, pp. 6–19.) These research methods, combined with animal models, have broad implications for screening males for chromosomal abnormalities and genetic diseases, for studying the effects of exposure to mutagenic agents, and for assessing genetic risks to embryos and offspring.

Even the food we eat can damage our DNA. Both 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyrinidine (PhIP) and 2-amino-3,8-dimethylimidazol [4,5-f] quinoxaline (MeIQx) are heterocyclic aromatic amines that appear in meat when it is cooked at high temperature. These compounds and others produced when they are digested form adducts, which are molecules that attach to DNA strands and may interfere with their function. Jim Felton, who is now deputy associate director for Biology and Biotechnology Research Program (BBRP), led a group studying food mutagens for almost two decades.

PhIP and MeIQx have been shown to cause cancer in laboratory animals when administered at high doses. More recently, researchers wanted to know whether DNA and protein adducts can be detected in laboratory animals and humans when they take in a smaller, more typical dietary amount of these substances. In numerous experiments using carbon-14-tagged PhIP and MeIQx molecules, the team has confirmed not only that adducts can be detected at low doses, but also that humans may be more sensitive to these substances than mice or rats.

Such experiments would not have been possible without Livermore's Center for Accelerated Mass Spectrometry. Physics-based accelerator mass spectrometry (AMS) is so sensitive that it can find one carbon-14 atom among a quadrillion other carbon atoms. It can observe the interaction of mutagens with DNA in the first step in carcinogenesis. Livermore is one of just a few institutions in the world using AMS routinely for biomedical and pharmaceutical applications, and it is a recognized leader in the field. (See *S&TR*, July/August 2000, pp. 12–19.)

Continuing a long tradition of collaboration with universities, Livermore joined forces with the University of California at Davis Cancer Center in October 2000 to fight



Meat cooked at high temperatures produces mutagens, which are compounds that can damage DNA. Here, a fully instrumented hamburger patty is fried to determine its temperature as a function of depth as well as the corresponding concentrations of food mutagens. The data are used to develop computer simulations of the cooking process and to predict the formation of mutagens.

cancer, the nation's second leading killer. Together, they are researching cancer biology, prevention, and control as well as new cancer detection and treatment techniques. In July 2002, the center attained National Cancer Center status from the National Cancer Institute. AMS is a key technology in this collaboration's research.

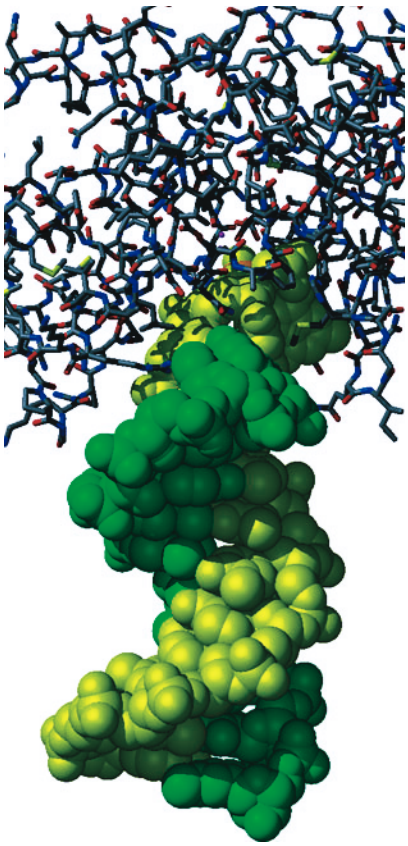
Putting the Computer to Work

Computers have played an integral role in biological research at Livermore for years (see the box on p. 26). In fact, the biomedical program was the first one at Livermore to purchase a personal computer for scientific use. The Procurement Department looked on this purchase with considerable suspicion, viewing a personal computer only as a means to play "Pong." But that little PC automated what had been a tedious manual cell-counting process, and it is impossible to imagine the Laboratory without desktop computers today.

Using both mainframe and personal computers, the Laboratory has pioneered many new ways to use the computer in a biological research setting. Bioinformatics is an area of special strength. In bioinformatics, computer scientists organize the results of molecular biologists' work, developing databases and new analytical tools so that the data can be put to good use. Livermore's leading role in the Human Genome Project would not have been possible without the efforts of BBRP's bioinformatics team. Computer scientist Tom Slezak started this group almost 25 years ago and still leads it.

"Our work is 'bottom of the iceberg' stuff and invisible to most people," says Slezak. "But it's really important. In sequencing the human genome, the flood of data was enormous. As other organisms are sequenced and as the field of comparative genomics takes off, we try to leverage our computational capabilities to stay a step or two ahead."

Computational biology, a relatively recent research area, builds on the Laboratory's strength in computations. According to Michael Colvin, who leads the Computational Biology Group at Livermore, "The emerging explanation of biological functions in terms of their underlying chemical processes is creating an important role for predictive chemical simulations in biological research."



This classical molecular dynamics simulation examines the motion of 1 of 10 proteins of *Escherichia coli* polymerase III, the major DNA replication enzyme in *E. coli* bacteria. This protein's function is to "proofread" a newly synthesized DNA strand by excising any incorrect bases immediately after they are added to the DNA. The goal of this simulation is to understand the chemical mechanism of the proofreading function. Shown as sticks is the proofreading protein. The yellow and green spheres simulate the double-stranded DNA being proofread.

The Handheld Advanced Nucleic Acid Analyzer can detect biological pathogens in the field. It examines the DNA of a sample and compares it with the known DNA sequence of various pathogens such as anthrax and plague. Rapid detection of agents of biological warfare could help save lives because the diseases resulting from many such pathogens are highly treatable if detected early.

Livermore scientists are at the forefront of integrating computation and experiment in bioscience. Ongoing computational biology projects include studying the action of anticancer drugs, DNA-binding properties of mutagens in food, the binding of ligands to selected sites on proteins, the mechanisms of DNA repair enzymes, and the biophysics of DNA base pairing. (See *S&TR*, April 2001, pp. 4–11.)

A particularly exciting tool in computational biology is first-principles quantum mechanics methods to describe the electronic structure of atoms and their chemical properties. Computerized quantum simulations permit researchers to "see" inside biochemical processes to learn how reactions are taking place on a molecular and even atomic level. Such simulations are highly intensive computationally and had to await the arrival of massively parallel computers before they could be performed. (See *S&TR*, April 2002, pp. 4–10.)

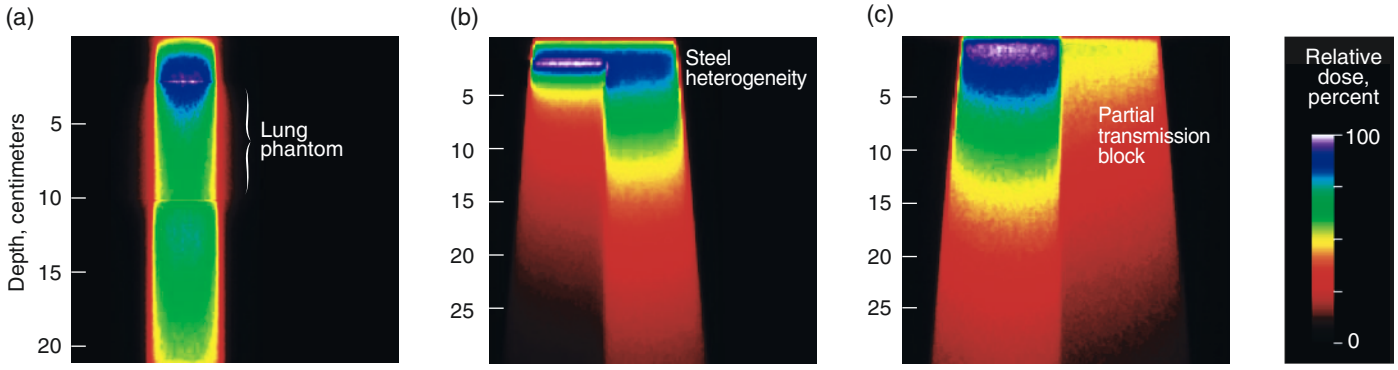
Fighting Bioterrorism

Bacteria, viruses, biological toxins, or genetically altered organisms could be used to threaten urban populations, destroy livestock, and wipe out crops. These agents are difficult to detect and to identify quickly and reliably. Yet, early detection and identification are crucial for minimizing their potentially catastrophic human and economic cost. At Livermore, developing technologies to detect agents of biological warfare has been under way for a decade. Livermore researchers pioneered technologies for rapid detection of tiny amounts of DNA. Equally important has been identifying specific DNA sequences that can be targeted with our detectors. With the recent anthrax attacks and the resulting awareness of bioterrorism threats, Livermore has stepped up its efforts to optimize stationary and portable equipment to detect biological agents.

The foundation for this research was laid during the early years of the program and studies of DNA. For example, by computationally comparing the DNA sequence of *Yersinia pestis*, the bacterium that causes bubonic plague, with the sequence of its close relatives and other bacteria, Livermore has been able to develop unique DNA signatures that allow *Yersinia* to be quickly detected. (See *S&TR*, May 2000, pp. 4–12.)

An entirely new sequencing analysis technique, developed by Livermore's bioinformatics team, recently won one of two 2002 Lawrence Livermore Science and Technology Awards. Using their experience from many years on the Human Genome Project, the team members found a novel way to perform whole genome analysis to compare genomic sequences. With it, they can rapidly determine unique DNA signatures of biowarfare pathogens. They are the first to apply whole genome analysis to pathogens.

Several DNA-detection technologies have been licensed to industry, most recently the Handheld Advanced Nucleic Acid Analyzer (HANAA). Some of these devices depend not only on accurate DNA signatures but also on microfluidics—the miniaturization of piping systems through which fluids flow. In a collaboration with Los Alamos National Laboratory, Livermore's DNA analysis capabilities were used to develop the analysis core of the Biological Aerosol Sentry and Information System, which was deployed at the 2002 Winter Olympics in Salt Lake City, Utah.



PEREGRINE is an innovative radiation planning technology developed at Livermore. Taken by the staff at the University of California at San Francisco, these images of PEREGRINE measurements demonstrate how effectively PEREGRINE can handle different materials and shapes, including (a) heterogeneous materials such as soft tissue and air in the lung, (b) a steel prosthesis, and (c) a partial transmission block that protects healthy tissue from radiation treatment.

Another technique for detecting biological agents focuses on detecting the proteins that DNA generates. Protein detection techniques are typically fast and easy to use but are not as sensitive and specific as DNA detection methods. Livermore is designing seek-and-destroy, antibodylike molecules, called high-affinity ligands, that target specific proteins in biological agents. The development of ligands for detecting tetanus toxin is almost complete. This detection methodology promises to be fast and easy to use as well as highly sensitive and specific. (See *S&TR*, June 2002, pp. 4–11.)

Physics to Biology

Many threads link physics advances and bioresearch progress. Ernest O. Lawrence, founder of the Laboratory, set the precedent for applying tools developed in the course of physics research to fighting human disease. After Lawrence built the cyclotron, he put it to use as a medical tool as quickly as he could. In 1937, Lawrence's mother Gunda was told by many specialists that she had an inoperable tumor. But her life was saved by radiation treatment with the only megavolt x rays then available in the world, using a device developed by her son. She was still living in Berkeley when he died 21 years later.

In this tradition, Livermore recently developed an innovative tool for analyzing and planning radiation treatment for tumors. In the early 1990s, researchers began combining Livermore's huge storehouse of data on nuclear science and radiation transport with Monte Carlo statistical techniques. The result was PEREGRINE, a radiation planning technology that has been licensed to a private company and was approved for use by the U.S. Food and Drug Administration in September 2000. (See *S&TR*, June 2001, pp. 24–25.)

Mrs. Lawrence's treatment and PEREGRINE bring the results of physics research to bear on a pressing medical challenge. Weapons materials have also been used in artificial hip joints designed at Livermore. X-ray tomography developed to examine the inner components of nuclear weapons has revealed the bone weakening of osteoporosis. Quantum simulations, a physics tool that can describe the fundamental interactions of weapons materials, are exposing the inner workings of biochemical processes important to human health. X-ray diffraction using synchrotron light sources, another physics tool, illuminates proteins to help define their function.

The next step in biological research will depend on another tool made possible by advanced physics research—even more powerful computers than are available today. "Where we're going next," says Bert Weinstein, acting associate director for BBRP, "is to understand the whole system of genes. Not just genes as individual parts but as an integrated, intermeshed set of molecular machines, working together to produce the miracle of life."

—Katie Walter

Key Words: accelerator mass spectrometry (AMS), biological warfare agent detectors, chromosome painting, comparative genomics, computational biology, DNA repair, dosimetry, flow cytometry, food mutagens, glycophorin-A assay, Human Genome Project, Joint Genome Institute (JGI), PEREGRINE, proteomics, sperm mutations.

For more information about Biology and Biotechnology Research Program Directorate:

www-bio.llnl.gov/

For details about the history of biology research at Livermore:

www-bbrp.llnl.gov/50_year_anniversary/

For frther information about the Laboratory's 50th anniversary celebrations:

www.llnl.gov/50th_anniv/